PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the ~~OJ 11/2001~~)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
R62598PC ih/gc		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/002920	18/03/2005	18/03/2004
International Patent Classification (IPC) or national classification and IPC		
C07C233/00		
Applicant		
REVOTAR BIOPHARMACEUTICALS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This **REPORT** consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of 6 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/01/2006	04.09.06
Name and mailing address of the IPEA/	Authorized officer
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Office européen des brevets · Europäisches Patentamt · European Patent Office

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-67 as originally filed

   Claims, Numbers

   1-10 filed with telefax on 18.01.2006

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-10
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 7

because:

☒ the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,5,6
	No:	Claims	1,2,4,7-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

This report is based in the application as originally filed. The reason therefore is that the amendments submitted by fax on 18.01.06 do not fulfil the requirements of Rules 19(2) and 34(2) b) PCT; the amendments excluding specific moities in X and selecting specific moieties in the general formulae have no basis in the application as filed, creating therefore subgroups which were not disclosed in the application as filed. These amendments go beyond the disclosure of the application as filed and are not allowed under Rules 19(2) and 34(2) PCT. Hence, this international preliminary report is based on the description and claims as originally filed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: US-B-6 340 7001 (AUGUET MICHEL ET AL) 22 January 2002 (2002-01-22)

D2: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002296238 retrieved from XFIRE accession no. BRN2765383

D3: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002296239 retrieved from XFIRE accession no. BRN2763456

D4: WO 99/29705 A2 (GLYCOMED INCORPORATED, USA; SANKYO CO., LTD.) 17 June 1999 (1999-06-17)

D5: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; NOMOTO, TAKASHI ET AL: "Preparation of hydroxybenzamide derivatives as prevention and treatment agents for bone

diseases" XP002296240 retrieved from STN Database accession no. 1996:513596

D6: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; NAKAJO, KYOSHI ET AL: "Silver halide color photographic material" XP002296241 retrieved from STN Database accession no. 1990:45554

D7: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SAKAGAMI, MEGUMI: "Silver halide color photographic material" XP002296242 retrieved from STN Database accession no. 1987:467992

D8: US-A-4 476 219 (KEI, SAKANOUE ET AL) 9 October 1984 (1984-10-09)

D9: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PASHCHENKO, E. N. ET AL: "Photometric determination of molybdenum in tungsten and its alloys as a carboxygallanilide complex" XP002296243 retrieved from STN Database accession no. 1976:536659

D10: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MAL'TSEV, V. F. ET AL: "Photometric determination of molybdenum" XP002296244 retrieved from STN Database accession no. 1975:612201

D11: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MORLYAN, N. M. ET AL: "N-(3,4,5-Trimethoxybenzoyl)-p-aminobenzoi c acid" XP002296245 retrieved from STN Database accession no. 1972:85515

D12: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SLYUSARE, A. T. ET AL: "Dissociation of p-carboxygallic anilide" XP002296246 retrieved from STN Database accession no. 1964:428806

D13: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; LAPIN, N. N. ET AL: "Determination of titanium in heat-resistant steels" XP002296247 retrieved from STN Database accession no. 1964:86480

D14: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SLYUSAREV, A. T. ET AL: "Dissociation of p-carboxygallanilide" XP002296248 retrieved from STN Database accession no. 1962:446636

D15: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE,

COLUMBUS, OHIO, US; MANNING, D. L. ET AL: "Association constants of silver(I) and cyanide ions in molten equimolar sodium nitrate-potassium nitrate mixtures" XP002296249 retrieved from STN Database accession no. 1962:446635

D16: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHINGAKI, TADAO: "Reaction of substituted benzazides with benzylamine" XP002296250 retrieved from STN Database accession no. 1961:22545

D17: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SLYUSAREV, A. T. ET AL: "Gallic acid anilides" XP002296251 retrieved from STN Database accession no. 1961:22544

D18: WO 2004/018502 A1 (YAMANOUCHI EUROPE B.V., NETH.) 4 March 2004 (2004-03-04)

D19: WO 97/01569 A (CIBA GEIGY AG ; KOLB HARTMUTH C (DE)) 16 January 1997 (1997-01-16)

D20: EP-A-1 081 151 (EISAI CO LTD ; MERCIAN CORP (JP)) 7 March 2001 (2001-03-07)

D21: WO 03/075905 A (LOPEZ-BELMONTE PASCUAL JUAN ; BOBEL 246 S L (ES); LOPEZ-BELMONTE PASCU) 18 September 2003 (2003-09-18)

D22: Journal of Biological Chemistry 2003, 278(12), 10201-10207; Appeldoorn, Molenaar, Bonnefoy et al.; XP002275710

1. The present application relates to pharmaceutical compositions comprising 2,3,4-trihydroxyphenyl-acetylamino;3,4-5-trihydroxyphenyl-acetylamino;2,3,4-trihydroxy-benzoylamino and 3,4,5-trihydroxy-benzoylamino derivatives and their use in the preparation of medicaments useful in the treatment of selectin-mediated diseases such as inflammatory disorders.

Lack of clarity, lack of disclosure and incomplete search and examination

2. Present claims 1-10 relate to an extremely large number of possible compounds/compositions and their use in medicine. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds claimed (those ones in the activity examples). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those

parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds disclosed in the activity examples.

In fact, the claims contain so many options, variables, possible permutations and different possibilities of attachment of the different options that a lack of clarity within the meaning of Article 84 EPC arises to such an extent as to render a meaningful search of the claims impossible. Consequently, as explained above, the search has been carried out for those parts of the application which do appear to be clear , namely the compounds in the activity examples and closely related homologous compounds; compounds according to formulae A2, B2 wherein Y' is as in claim 2 with R^{10} and R^{11} being CO_2H or CO_2alkyl.

Novelty

3. The subject-matter of claims 1, 2, 4 and 7-10 is not novel in the sense of Art.33(2) PCT.

3.1. D1 discloses compound with rn 214124-47-7: benzamide, N-[2-(4-aminophenylethyl]-3,4,5-trihydroxy and its use in medicine in the treatment of inflammatory processes. This disclosure is novelty destroying for the subject-matter of claims 1, 2, 4 and 7-10, which is therefore not novel.

3.2. D2 discloses N-(4-diethylamino-phenyl)-3,4,5-trihydroxy-benzamide. This disclosure anticipates the subject-matter of claims 1, 2 and 4, which is therefore not novel.

3.3. D3 discloses N-(4-dimethylamino-phenyl)-3,4,5-trihydroxy-benzamide. This disclosure anticipates the subject-matter of claims 1,2 and 4, which is therefore not novel.

3.4. D4 discloses the compounds 4-piperidinecarboxylic acid, 1-(3,4,5-trihydroxybenzoyl), rn:227462-58-0 and 4-piperidineacetic acid, 1-(3,4,5-trihydroxybenzoyl) and their use in the treatment of selectin-mediated disorders. This disclosure anticipates the subject-matter of claims 1, 2, 4 and 7-10, which is therefore not novel.

3.5. D5 discloses benzoic acid, 3-[(2,3,4-trihydroxybenzoyl)amino]-ethyl ester, rn:180205-92-9 and benzoic acid, 3-[(2,3,4-trihydroxybenzoyl)amino], rn: 180206-22-8 and their use in the prevention and treatment of bone diseases. This disclosure anticipates the subject-matter of claims 1, 2 and 4, which is therefore not

novel.

3.6. D6 discloses benzoic acid, 4-chloro-3-[(3,4,5-trihydroxybenzoyl)amino]-dodecyl ester, rn:89946-84-9 and benzoic acid, 4-[(3,4,5-trihydroxybenzoyl)amino]-hexadecyl ester, rn:124709-44-0. This disclosure anticipates the subject-matter of claims 1, 2 and 4, which is therefore not novel.

3.7. D7 and D8 disclose benzoic acid, 4-chloro-3[(3,4,5-trihydroxybenzoyl)amino]-dodecyl ester, rn: 89946-84-9. These disclosures anticipate the subject-matter of claims 1, 2 and 4, which is therefore not novel.

3.8. D9-D17 disclose benzoic acid, 4-[(3,4,5-trihydroxybenzoyl)amino], rn: 35388-09-1. Theses disclosures anticipate the subject-matter of claims 1, 2 and 4, which is therefore not novel.

Inventive step

4. The subject-matter of claims 3, 5 and 6 cannot be considered to involve an inventive step in the sense of Art.33(3) PCT.

4.1. The use of 2,3,4-trihydroxyphenyl-acetylamino;3,4-5-trihydroxyphenyl-acetylamino;2,3,4-trihydroxy-benzoylamino and 3,4,5-trihydroxy-benzoylamino derivatives and gallic acid derivatives in the treatment of selectin-mediated diseases and more specifically in the treatment of inflammatory disorders is well known in the art (D1, D4, D18-D20 and D22). A very broad variety of these compounds are disclosed therein for the above-mentioned medical disorders.

4.2. The problem to be solved in claims 3, 5 and 6 is seen in the provision of alternative selectin inhibitors.

4.3. Claims 3, 5 and 6 embrace a huge number of compounds/compositions wherein the compounds differ from each other as much as from the compounds in the prior art D1, D4, D18-D20 and D22. Hence, in view of the same activity for compounds which are as well 2,3,4-trihydroxyphenyl-acetylamino; 3,4-5-trihydroxyphenyl-acetylamino; 2,3,4-trihydroxy-benzoylamino; 3,4,5-trihydroxy-benzoylamino and gallic acid derivatives, it would be obvious for the skilled person in the art the provision of alternative compounds belonging to the same category and would arrive to the

compounds in claims 3, 5 and 6.

4.4. Furthermore, in view of the activity tests, only a very few compounds have been tested; therefore, the huge scope of the claims 3, 5 and 6 does not seem justified.

Further comments

5. For the assessment of the present claim 7 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

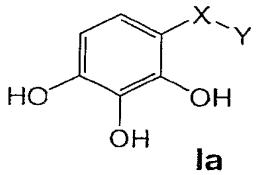
6. To meet the requirements of Rule 27(1)(b) EPC, the documents D1, D4 and D18-D20 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

New set of claims
PCT/EP2005/002920

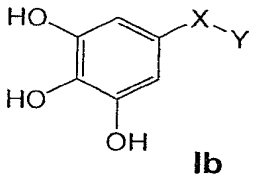
January 18, 2006

Claims

1. Pharmaceutical compositions comprising at least one compound of the formulas (Ia) or (Ib) and a pharmaceutically acceptable carrier which is useful in a medicine.

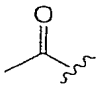


Ia

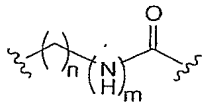


Ib

wherein symbols, indices and substituents have the following meaning

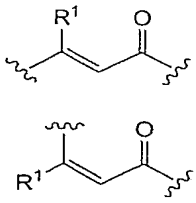
(-X- in case of  or  with T being O as part in -X-, the orientation of -X- is limited to the variant where the carbonyl function is directly connected with -Y) =

(a)



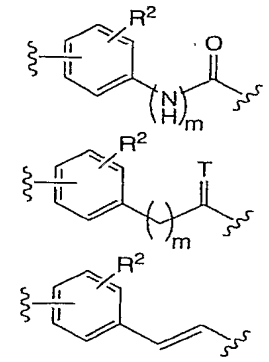
with m = 0,1; n = an integer from 1 to 3

(b)

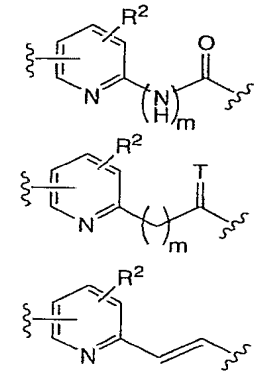


with R^1 being H, CH_3, CH_2CH_3

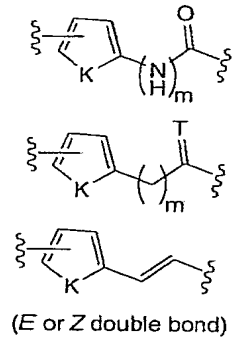
c)



(*E* or *Z* double bond)



(*E* or *Z* double bond)

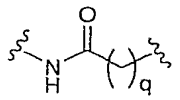


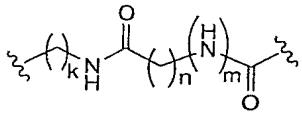
(*E* or *Z* double bond)

with R^2 being H, NO_2, CF_3, F, Cl, Br, I, CN, CH_3, NH_2, NHAlkyl, NHAryl, NHAcyl and -K- being -S- or -O-

and T being O or [H,H]

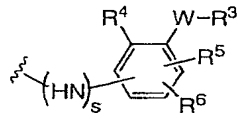
(d)

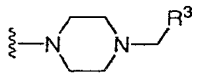


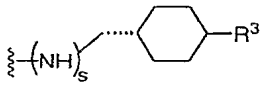


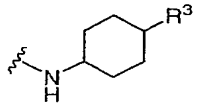
with k=0, 1, 2 and with q being an integer from 1 to 3

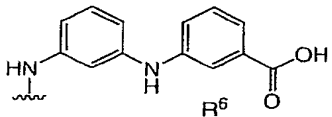
-Y =

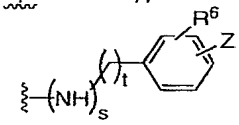












with s being 0 or 1,

R^3 being CO_2H, CO_2Alkyl, CO_2Aryl, CO_2NH_2, $CO_2Aralkyl$, SO_3H, SO_2NH_2, $PO(OH)_2$, 1-H-tetrazolyl-, CHO, $COCH_3$, CH_2OH, NH_2, NHAlkyl, N(Alkyl)Alkyl', OCH_3, CH_2OCH_3, SH, F, Cl, Br, I, CH_3, CH_2CH_3, CN, CF_3

R^4 independently from R^3 being H, CH_3, CH_2CH_3, CF_3, F, Cl, Br, I, CN, NO_2 and

R^5 independently from R^3 and R^4 being H, CH_3, CH_2CH_3, NO_2, R^3

R^6 being H, NO_2, CF_3, F, Cl. Br, I, CN, CH_3, OCH_3, SH, NH_2

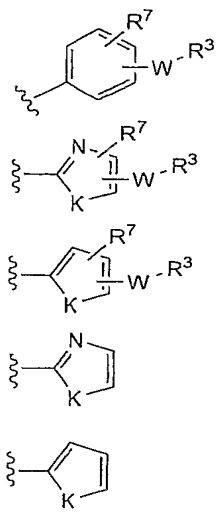
t being 0,1,2

and -W- = $-(CH_2-)_v$, *cis*-CH=CH- or *trans*-CH=CH-, and v being 0,1,2;

in case that $R^3 = NH_2$ R^4 or R^5 or R^6 must not be H;

in case that -W- is *cis*-CH=CH- or *trans*-CH=CH-, R^3 must not be NH_2 or SH;

-Z =

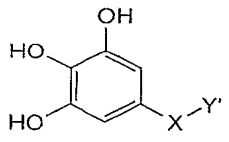


-W-R^3

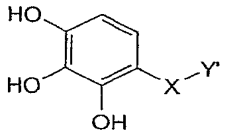
R^7 independently from R^6 being H, NO_2, CF_3, F, Cl. Br, I, CN, CH_3, OCH_3, SH, NH_2,

or the pharmaceutically acceptable salts, esters or amides and prodrugs of the above identified compounds of formulas (Ia) or (Ib).

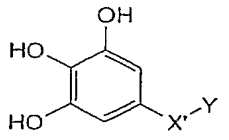
2. Pharmaceutical compositions according to claim 1, wherein the compounds are defined by formulas (A1), (B1), (A2) or (B2)



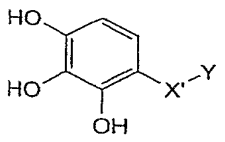
A1



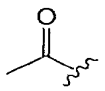
B1



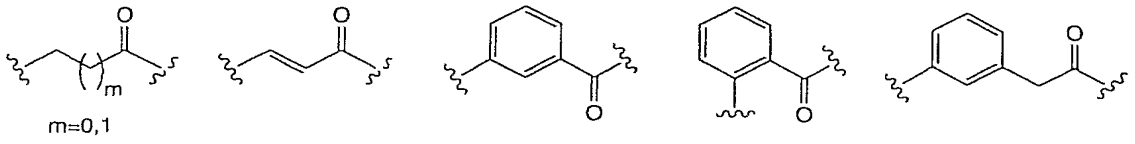
A2



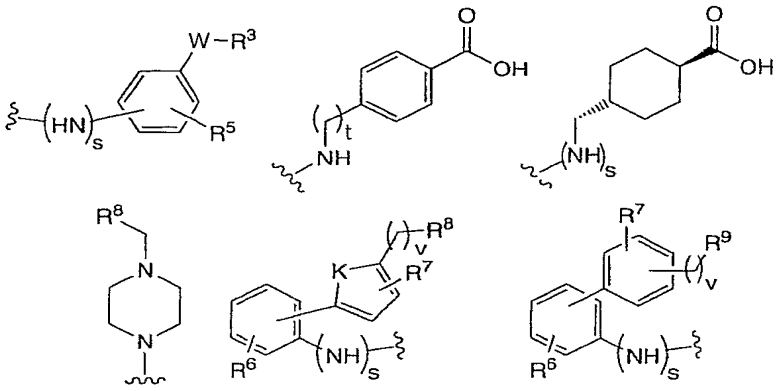
B2

wherein -X- and -Y are like defined above and wherein -X'- is (in case of  as part in -X'-, the orientation of -X'- is limited to the variant where the carbonyl function is directly connected with -Y)

is



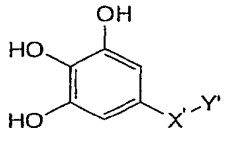
and wherein -Y' is



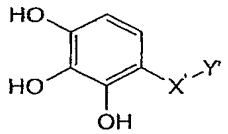
with R^8 being CO_2H, CO_2alkyl, CO_2aryl, CO_2NH_2, CO_2aralkyl, CH_2SO_3H, $CH_2SO_2NH_2$, $CH_2PO(OH)_2$, 1-H-tetrazolyl, CHO, $COCH_3$, CH_2OH, CH_2NH_2, CH_2NHalkyl, CH_2N(alkyl)alkyl', CH_2OCH_3, CH_2SH,

R^9 being CO_2H, CO_2alkyl, CO_2aryl, CO_2NH_2, CO_2aralkyl, SO_3H, SO_2NH_2, $PO(OH)_2$, 1-H-tetrazolyl, CHO, $COCH_3$, OH, NH_2, NHalkyl, N(alkyl)alkyl', OCH_3, SH

3. Pharmaceutical compositions according to claim 1, wherein the compounds are defined by formulas (C) or (D)



C



D

wherein -X'- and -Y' are defined like in claim 2.

4. Pharmaceutical compositions according to claim 2 and/or 3, comprising at least one compound of formula (A1), (A2), (B1), (B2), (C) or (D).

5. Compounds according to claim 3 having the general structure of formula (C).

6. Compounds according to claim 3 having the general structure of formula (D).

7. Method of inhibiting the binding of P-selectin, L-selectin or E-selectin to sLe^x or sLe^a and tyrosinesulfate residues comprising the step of administering to a patient an effective amount of at least one compound having the structure of formulas (Ia) or (Ib) as defined in claim 1.

8. Use of compounds having the structure of formulas (Ia) or (Ib) as defined in claim 1 for the preparation of a medicine for the treatment of a patient, inhibiting the binding of P-selectin, L-selectin or E-selectin to sLe^x or sLe^a and tyrosinesulfate residues.

9. Use of compounds having the structure of formulas (Ia) or (Ib) as defined in claim 1 for the preparation of a medicine for the treatment, diagnosis or prophylaxis of inflammatory disorders and other medical conditions where selectin mediated processes play a role.

10. Use of compounds having the structure of formulas (Ia) or (Ib) as defined in claim 1 for the preparation of a vehicle for drug targeting of diagnostics or therapeutics.